Results of Long-Continued Cortisone Administration in Rheumatoid Arthritis

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SUMMARY

The administration of cortisone acetate to patients with rheumatoid arthritis usually produces prompt and often dramatic suppression of the disease manifestations. The effects of the hormone are not lasting, however, and after withdrawal relapse ensues. For sustained improvement in a chronic disease such as rheumatoid arthritis, it appears that cortisone must be given more or less continuously. This raises the question whether administration may be continued effectively and safely for long periods.

Seventy-six patients with rheumatoid arthritis were given cortisone in the hope that treatment could be continued uninterruptedly for extended periods. For various clinical reasons it was necessary to discontinue treatment in 16 of these before six months, but the remaining 60 patients received the hormone uninterruptedly for six to 15 months. By using initial large suppressive amounts, then gradually reducing the dosage, and finally employing smaller maintenance doses, adequate degrees of rheumatic control were maintained in approximately two-thirds of the original 76 patients. The ability to sustain satisfactory improvement varied indirectly, in general, with the severity of the rheumatoid arthritis. The chief detriment to better results in the more severe cases was the intervention of adverse hormonal side effects which developed frequently when large or relatively large maintenance doses were required to support satisfactory improvement.

Unwanted signs of hormonal excess developed in 40 per cent of cases at some time during the course of treatment. Most of them were mild or transient and disappeared or lessened when the dose of cortisone was reduced, but when the dose was reduced the degree of improvement often declined also.

During prolonged cortisone therapy evidence of functional suppression of the adrenal cortices, as indicated by a decreased response of circulating eosinophils to exogenous ACTH, was present. The depression of cortical function was temporary, however. Whether irreversible damage may result when the drug is employed for longer periods cannot yet be answered.

WHEN cortisone acetate is administered in adequate doses to patients with active rheumatoid arthritis, prompt and often dramatic improvement of the clinical and certain laboratory manifestations of the disease results. Articular pain, stiffness and tenderness are diminished with impressive consistency and such reversible changes as articular or bursal effusion, periarticular swelling, muscle weakness and atrophy, subcutaneous nodules, mild flexion contractures, low-grade fever, weight loss, anemia and accelerated erythrocyte sedimentation rates are corrected or reduced. Unfortunately, however, the effects of cortisone are not lasting and, with almost as impressive consistency, the disease manifestations reappear when the hormone is withdrawn. For sustained improvement the drug must be given more or less continuously. The ultimate course of rheumatoid arthritis is probably not altered significantly by cortisone and the beneficial effects from its administration reflect a suppressive, not a curative, influence.

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Patients with rheumatoid arthritis apparently have normally functioning adrenal glands[8, 12] as indicated by lack of clinical signs of adrenocortical insufficiency and absence of evidence of hormonal deficiency from the various tests now available.[14] The amounts of cortisone needed for satisfactory antirheumatic response are large and probably greater than the quantities of corticosteroids which the patient's own adrenal glands would supply in normal circumstances. Hence the improvement which results from cortisone administration does not represent correction of a glandular deficiency by substitution therapy but rather a favorable effect from an exogenously induced state of hormonal excess. Cortisone exerts potent influences on the functions of many organs and tissues, and with its continued administration unfavorable hyperadrenocortical effects may also be promoted. Aside from the beneficial action on rheumatic manifestations, such unwanted signs of hypercortisonism as disturbances in electrolyte, water and carbohydrate metabolism, skin changes such as hypertrichosis, acneiform eruption, pigmentation and striae, abnormal fat deposition, menstrual disorders, mental

changes and retardation of wound healing may develop with its use.

Since the suppressive influence of cortisone endures for only as long as the drug is being given, and since rheumatoid arthritis is a chronic and often progressive disease, it would appear necessary to maintain therapy indefinitely, at least in most cases, if improvement is to be sustained. The practicability of employing cortisone continuously for long periods raises three main questions: (1) Can the antirheumatic action of the hormone be maintained with long-continued use, or will improvement eventually deteriorate and relapse occur? (2) Can administration be continued for long periods without causing significant hormonal side reactions? (3) Will prolonged uninterrupted treatment produce irreversible damage to vital organs, especially permanent impairment of adrenocortical function? With a view to obtaining information which might aid in answering these questions, an investigation of the effects of uninterrupted cortisone therapy in patients with rheumatoid arthritis was begun in January 1950.

PRELIMINARY STUDY

In September 1950 preliminary observations with regard to 42 patients treated continuously with cortisone acetate given intramuscularly for periods ranging from two to six months were reported.[1] The dosage plan followed consisted of three stages: (1) period of initial large suppressive doses; (2) period of gradual dose reduction; and (3) period of extended smaller maintenance dose administration. Initial suppressive doses were given until the clinical manifestations were brought under control. For severe and moderately severe cases 200 or 300 mg. of the hormone was administered on the first day, followed thereafter by daily injections of 100 mg.; for moderate and mild cases, 100 mg. was given on the first and subsequent days. When rheumatic activity had been suppressed satisfactorily by 100 mg. doses, the daily amounts of cortisone were then reduced gradually in a step-like fashion, reductions being made by 5 to 10 mg. per dose at intervals of every five to seven days. The smallest daily amount of cortisone required to maintain adequate, although not necessarily absolute, control was considered as the maintenance dose for the patient. The maintenance dose was then continued, with adjustments in the daily amounts being made from time to time as changes in the clinical response or the development of objectionable reactions dictated. Sustained complete remission of the disease was not sought; it was found more prudent at times to be content with satisfactory improvement short of adverse effects rather than to strive for total suppression with larger and unsafe doses.

By first suppressing the disease with large doses of the hormone it was possible to retain control with smaller maintenance doses in 32 (76 per cent) of the 42 patients. The size of the maintenance dose required for control depended chiefly on the severity of the rheumatoid arthritis. In general, more of the hormone was needed in severe cases than in less severe cases: With average daily doses of 50 mg. or less given intramuscularly, for example, adequate suppression of the disease was maintained in 100 per cent of mild cases, 89 per cent of the moderate, 53 per cent of the moderately severe, and in only 7 per cent of the severe. The incidence of unwanted hormonal effects was decidedly less when smaller daily amounts of the drug were used; signs of hypercortisonism developed in only 8.3 per cent of patients when the daily dose was 65 mg. or less and in 33 per cent when doses of 100 mg. daily were employed. Because the periods of observation were relatively short (two to six months) the question as to whether cortisone could be administered safely and effectively for periods of many months or years could not be positively answered.

PRESENT STUDY

The observations to be reported herein result from a continuation and expansion of the previously reported investigation. With the hope of administering cortisone uninterruptedly for prolonged periods in each instance, 76 patients with chronic rheumatoid arthritis were started on treatment between January 1 and September 1, 1950. In 16 cases treatment was stopped for various clinical reasons within the first six months. The remaining 60 patients, however, have received cortisone continuously for longer than six months, and 27 of them for periods exceeding one year. Experiences with these 60 patients constitute the principal basis for this report.

Selection of Patients: Of the 76 patients, 45 were women and 31 were men. Ages varied from 19 to 80 years. The arthritis was restricted to peripheral joints in 56 patients, to the spine in 3, and 17 had combined involvement of the peripheral joints and the spine. The average duration of the disease for the group was 7.2 years with a range from seven months to 26 years. All patients had active disease and acceleration of the erythrocyte sedimentation rate, although they presented varying degrees of functional impairment and structural change. The rheumatoid arthritis was classified as severe in 36 patients, moderately severe in 27, moderate in 12, and mild in one.

Manner of Administration: During the early months of the investigation all patients received the hormone by intramuscular injection. Since June 1950 most patients have been given the drug by mouth, either in tablet form or as a liquid prepared by mixing the suspension, as supplied for parenteral use, with a flavored syrup. Fifty-four of the 60 patients treated for long periods have received oral preparations. Most of those initially treated by the intramuscular route were transferred to oral medication, and all of those started on cortisone since June 1950 have received the drug by mouth. When comparing statistics dealing with dosage requirements, it must be kept in mind that the amount of cortisone needed by mouth for equivalent anti-

rheumatic control may be larger than the amount needed when it is given by intramuscular injection; the oral requirement may be one-fifth to one-third greater.[2]

The same general dosage plan, as described under the preliminary study, was adhered to regardless of the route of administration. Results were decidedly best when full suppressive amounts of the hormone were given at the beginning of treatment and the dose then gradually reduced until the smallest dose needed to control the manifestations was reached. With oral preparations, gradual step-down of dosage was accomplished by reducing the amount 12.5 mg. at a time at intervals of every five to seven days. The amount prescribed orally was usually taken in divided doses four times daily; and intramuscular injections, when used, were given daily or every other day. Most patients were treated in the office from the beginning, but a few with severe disease were hospitalized for short periods initially.

Grading of Results: The response to therapy was graded on the basis of objective and subjective improvement into five categories: very pronounced, pronounced, moderate, slight, and unimproved.[1, 8] To retain a very pronounced degree of improvement in severe and moderately severe cases, it may be necessary to employ large daily maintenance doses of the hormone. With the long-continued use of large doses, such as 100 to 150 mg. per day, however, troublesome signs of hormonal excess are frequent and often they become so pronounced as to necessitate discontinuation of treatment. After large daily amounts of cortisone had been given as early suppressive therapy, attempt then was made to use the minimum dose required for satisfactory, not necessarily total, control of the disease. By such a plan it was hoped to prevent, as far as possible, serious signs of hypercortisonism. The degree of sustained improvement from maintenance doses was considered adequate if the patient was able to perform his normal business or duties comfortably without analgesics, but with perhaps some restriction in physical activity. In most instances "adequate control" was equivalent to improvement graded as pronounced or better.

RESULTS OF PROLONGED CORTISONE ADMINISTRATION ON RHEUMATIC MANIFESTATIONS

The maintenance dosage requirements and the degrees of clinical improvement were subject to variations from time to time in many patients, but these can be dealt with herein only in generalities. The statistics presented are based on clinical evaluations completed on March 31, 1951, and undoubtedly they will differ from results compiled at a later date when this group of patients has been followed longer.

Over-all Results: As was noted previously, cortisone therapy was stopped within the first six months in 16 cases. The reasons were as follows: (1) In eight patients the degree of improvement was not sufficient, even with the use of large daily doses, to warrant prolongation of treatment. In four patients the improvement was never more than moderate, and in two (both with spondylitis only) no improvement at all was noted. Two patients experienced excellent early response but after two and four months, respectively, relapse occurred despite increasing amounts of the hormone. Five of the eight patients had very severe rheumatoid arthritis, and whereas massive doses of cortisone might have produced better results, long-continued use of the hormone in such amounts would have been unsafe and hence impractical. (2) In seven instances the drug was stopped because unduly troublesome hyperadrenocortical effects developed. In five of these cases the patients had severe disease and desired degrees of relief could not be supplied with daily doses small enough to avoid side reactions. (3) One patient experienced complete clinical remission after four months of treatment. The dosage was gradually lowered and finally administration was discontinued. Remission lasted for nearly five months but then gradual recrudescence ensued and recently treatment was resumed.

The remaining 60 patients were treated without interruption for periods ranging from six to 15 months. A satisfactory degree of improvement (pronounced or very pronounced) was maintained in 48 of the patients; the other 12 remained improved but the degrees of control were considered minor and inadequate (Table 2).

If the entire original group of 76 patients is considered (and if one patient who had remission is excluded), the manifestations of rheumatoid arthritis were held under satisfactory suppression for long periods with maintenance doses of cortisone in slightly less than two-thirds (48 of 75) of the patients (Table 1).

General Results in Patients Treated for Periods of Six Months or Longer: In the 60 cases in which treatment was continued for periods of six to 15 months, the degree of improvement maintained was

TABLE 1.—*Cortisone Therapy in Rheumatoid Arthritis: Overall Results in Entire Series of 76 Patients*

Severity of Disease	No. of Cases	Adequate Anti-rheumatic Control for 6 Months or Longer		Inadequate Anti-rheumatic Control but Therapy Continued for 6 Months or Longer		Cortisone Discontinued Before 6 Months			
		No.	Per Cent	No.	Per Cent	Inadequate Initial Response	Early Deterioration of Improvement	Adverse Hormonal Reactions	Clinical Remission
Severe	36	17	47.2	8	22.2	5	1	5	0
Moderately Severe	27	19	70.4	4	14.8	1	1	1	1
Moderate	12	11	91.7		0	0	0	1	0
Mild	1	1	100		0	0	0	0	0
Totals	76	48	63.2	12	15.8	6	2	7	1

graded as very pronounced in 18 (30 per cent), pronounced in 30 (50 per cent), moderate in 11 (18.3 per cent), and slight in one (1.7 per cent) (Table 2).

Of the 12 patients who retained only minor degrees of improvement, five had adverse effects from the drug which prevented the use of doses sufficient for proper regulation of the disease, and five (three with severe and two with moderately severe rheumatoid arthritis) had no more than moderate improvement even with full amounts of the hormone. In the remaining two patients excellent control was sustained for ten and thirteen months, respectively, on doses averaging 37.5 to 62.5 mg. per day; and then, for no apparent reason, relapse occurred and increasing amounts of cortisone, up to 125 mg. per day, did not reestablish satisfactory response.

Results in Relation to Severity of Disease: It has been reported previously that the results from both large initial suppressive and from smaller maintenance doses of cortisone are distinctly better in patients with less severe rheumatoid arthritis.[1] Actually, the likelihood of promoting and retaining major degrees of improvement depends more on the severity of the disease than on any other single factor. In some severe cases adequate relief is not obtained even with large amounts of the hormone, while in others in which there is excellent response the patient cannot tolerate the required large doses for long periods because of attendant objectionable hormonal reactions.

In the 25 severe cases treated for more than six months, pronounced improvement was preserved in 16 and very pronounced improvement was upheld in only one (Table 2). The rheumatoid arthritis was graded as severe in 36 of the original 76 cases in the series—and in 11 of these cases treatment was stopped before six months either because of insufficient improvement or adverse reactions. For the whole series, therefore, less than one-half of severe cases (17 of 36) were adequately controlled by long-term therapy.

In the moderately severe classification, very pronounced or pronounced improvement was maintained in 19 of the 23 (82.6 per cent) cases treated for a long period and in 19 of the 27 (70 per cent) original cases.

The best results were obtained in cases of less severe rheumatoid arthritis: Pronounced or very pronounced improvement was obtained in all cases of moderate or mild degree of severity treated for a long period, and in 11 of the 12 original cases so graded.

Size and Stability of Maintenance Doses: Although there were notable exceptions, the daily amounts of cortisone required to support satisfactory regulation of the rheumatoid arthritis varied directly with the severity of the disease—in general, the more severe the disease, the more cortisone required. The average daily maintenance dose for the various groups was as follows: severe, 80.5 mg.; moderately severe, 64.1 mg.; moderate, 55.4 mg.; mild, 37.5 mg. (Table 1). The average dosage for severe and moderately severe cases would have been higher if the amounts needed for satisfactory results could have been given in all cases; this was not possible, however, as the dosage frequently had to be modified, with detriment to antirheumatic control, because of the advent of adverse reactions. The tabulated dosages are for oral administration in the majority of cases (54 of 60) and the average requirements are probably slightly higher than they would be for a comparable group treated wholly by parenteral injection.

During the course of observation variations in the amounts of cortisone needed for control were common and in most cases it was necessary to change the dosage from time to time. In 36 of the 60 patients (60 per cent) dosage requirements were quite stable and only minor adjustments were needed periodically. In nine cases the dosage remained fairly constant except that temporary exacerbations occurred on one or more occasions which required "booster doses" for the resumption of adequate control. Booster doses usually consisted of 100 or 125 mg. of cortisone daily for four or five days, followed by gradual reduction to the previous level. The need for temporary increases was at times provoked by some additional stress such as physical overactivity, emotional upset, intercurrent infection and fatigue. At other times departures from the usually required amounts appeared to be caused by spontaneous changes in disease activity.

In four patients the amounts of hormone needed fluctuated rather widely from time to time. One patient with moderately severe rheumatoid arthritis, for example, remained under almost complete con-

TABLE 2.—*Long-Continued Cortisone Therapy in Rheumatoid Arthritis: Results in Patients Treated Uninterruptedly for 6 to 15 Months*

Severity of Disease	No. of Cases	Maintenance Dose Required (mg.) Average for Group	Range	Degree of Improvement Maintained: Very Pronounced No.	%	Pronounced No.	%	Moderate No.	%	Slight No.	%	Degree Improvement Judged Adequate: Adequate No.	%	Inadequate No.	%	Adverse Hormonal Effects No.	%
Severe	25	80.5	37.5-125	1	4	16	64	7	28	1	4	17	68	8	32	14	56
Moderately Severe	23	64.1	37.5-100	8	34.8	11	47.8	4	17.4	0		19	82.6	4	17.4	8	34.8
Moderate	11	55.4	37.5-75	8	72.7	3	27.3	0		0		11	100	0		2	18.2
Mild	1	37.5	37.5	1	100	0		0		0		1	100	0		0	
Totals	60	68.8	37.5-125	18	30	30	50	11	18.3	1	1.7	48	80	12	20	24	40

trol for eight months on maintenance amounts averaging 50 mg. per day. For no apparent reason the cortisone requirement increased and for the next four months daily doses of 100 to 125 mg. were used. The requirement then gradually lessened and for three months up to the time of this report excellent antirheumatic effect has been maintained with 37.5 to 50 mg. a day. Such variations in dosage may well be due to spontaneous fluctuations of disease activity. Not infrequently the course of rheumatoid arthritis is subject to ups and downs of activity, and when this occurs it is reasonable to expect that the dosage requirement of a suppressive drug would vary with natural oscillations of the disease.

In five patients the cortisone requirement gradually increased over the months. The initial response to suppressive doses was excellent in each instance and good control was maintained on fairly stable doses for long periods. Deterioration of improvement then began and increasing amounts of the hormone were needed to support relief. Two patients became more and more active physically and, disregarding advice, assumed additional business responsibilities; but no reason for the declension of results was elicited in the other three. In two patients the disease finally became refractory to even large doses and eventually cortisone administration was stopped after 10 and 13 months, respectively, of continuous therapy.

In six patients, after long periods on relatively constant doses, there was gradual decrease in the amounts of cortisone needed. Maintenance doses as low as 25 mg. per day finally became sufficient for three patients and, with the hope that remission might continue, treatment was stopped after seven, nine, and ten months respectively; relapse occurred in one patient after two months, in another after seven weeks, and in the third withdrawal has been too recent to permit comment.

ADVERSE EFFECTS FROM PROLONGED CORTISONE ADMINISTRATION

Twenty-four (40 per cent) of the 60 patients had undesirable hormonal side effects at some time during the course of administration. Twelve had a single abnormality and 12 had multiple reactions; a total of 45 adverse signs were observed in the group. In many instances the signs of cortisone excess were of minor order or transient and were considered of little or no consequence by both the patients and the authors. Of the 45 side effects, 31 were graded as mild, 13 as moderate, and one (spontaneous vertebral fracture) as severe. In two patients the signs became sufficiently troublesome to necessitate cessation of therapy, after seven months of administration in one and after 11 months in the other.

As has been reported previously, unfavorable reactions are fewer and usually less pronounced when smaller doses of cortisone are used.[1] Of the 24 patients who had side effects, 17 were being maintained with total daily doses of 75 mg. or more, six were receiving 62.5 mg. per day, and one was being given 50 mg. daily. Because, in general, the amount of cortisone needed for suppression varies directly with the severity of the disease, the incidence of untoward reactions was higher in the more severe cases.

The individual adverse hormonal reactions which were observed are listed in Table 3. Experiences with them differ little from those reviewed previously by the authors[1, 3, 4] and by other investigators,[6, 8, 9, 12] so only a few will receive comment. The most common abnormalities were rounding of the facial contour, and edema. Both of these conditions usually responded readily to dosage reduction, and the elimination of water could be hastened with saline or mercurial diuretics. The occurrence of significant edema may be largely avoided by placing patients on a salt-poor diet from the start of treatment. Mild to moderate hypertrichosis developed in seven women; in two it became cosmetically troublesome and the excess facial hair was removed by electrolysis. As experience with cortisone has enlarged, fewer instances of undue psychic stimulation have been encountered; use of the drug is now avoided in patients with psychotic histories or with overt emotional instability. Also, mental stimulation and insomnia are less when smaller maintenance doses are employed and, it is believed, when oral medication is used.

Two other reactions deserve mention. Significant decreases in glucose tolerance developed in three patients, one with a normal pretreatment tolerance curve and two with latent diabetes beforehand. Each patient has had occasional glycosuria, but with moderate qualitative carbohydrate restriction (and without insulin) the abnormalities have been well controlled. One patient had spontaneous fracture of the twelfth dorsal vertebra after 53 days of treatment; he had coexistent latent diabetes mellitus and pronounced osteoporosis of the spine before treatment. The fracture responded favorably to orthopedic management and cortisone was not discontinued. Spontaneous fractures have been reported by other investigators.[7, 11] Spinal roentgenograms for osteoporosis should be made in any case in which the candidate for cortisone or ACTH therapy is elderly.

EFFECTS OF PROLONGED CORTISONE THERAPY ON ADRENOCORTICAL FUNCTION

Certain laboratory and clinical observations suggest that cortisone causes a temporary depression of adrenocortical function. During administration there is a reduction in the urinary excretion of 17-ketosteroids[8, 13] and, as gauged by the eosinopenic test, there is a diminished response to pituitary adrenocorticotropic hormone.[13] Immediately or soon after the withdrawal of cortisone, some patients complain of weakness and exhaustion and these symptoms have been interpreted as being due to adrenocortical insufficiency.[8, 13] With short-term or relatively short-term administration, the abnormalities have been temporary; at varying intervals following cessation of treatment, asthenia has disappeared and the results of tests have reverted to

TABLE 3.—*Individual Adverse Hormonal Side Reactions in Patients Receiving Continuous Cortisone Therapy for 6 to 15 Months*

Case No.	Sex	Average Daily Dose at Onset (mg.)	Onset in Relation to Length of Treatment			Severity of Reaction	Type of Reaction												Fate of Reaction on Continued Treatment			
			Before 3 Months	Between 3 and 6 Months	After 6 Months		Fracture	Purpura	Pigmentation	Mooning of Face	Skin Tags	Thyroid Enlargement	Nervousness	Edema	Menstrual Disturbance	Acne	Hypertrichosis	Decreased Glucose Tolerance	Progressed	Stationary	Improved	Disappeared
1	M	75.0	+			Mild												+		+		
2	F	75.0		+		Mild											+		+			
3	F	75.0	+ (1, 2, 3, 4)*			Mod. (1, 2, 3, 4)					+ (4)	+ (3)	+ (2)	+ (1)					+ (3&4)		+ (2)	+ (1)
4	M	100.0		+ (1, 2, 3, 4)		Mod. (1 & 2) Mild (3 & 4)			+ (4)	+ (1)			+ (2)			+ (3)				+ (1&4)	+ (2)	+ (3)
5	F	87.5		+		Mild				+										+		
6	M	75.0	+ (1 & 2)			Mild (1 & 2)				+ (1)						+ (2)					+ (1&2)	
7	M	100.0			+	Mild				+										+		
8	F	100.0 (1&2) 62.5 (3&4)	+ (1 & 2)		+ (3 & 4)	Mod. (1 & 2) Mild (3 & 4)		+ (2)		+ (4)				+ (1)			+ (3)		+ (3&4)			+ (1&2)
9	F	75.0			+	Mild											+		+			
10	F	100.0	+ (1 & 2)			Mod. (1) Mild (2)				+ (2)				+ (1)						+ (2)	+ (1)	
11	M	75.0	+ (4)	+ (1 & 2)	+ (3)	Mild (1) Sev. (2) Mild (3)	+ (2)			+ (1)	+ (3)							+ (4)	+ (3)	+ (4)	+ (2)	+ (1)
12	F	75.0	+ (1)	+ (2)		Mod. (1) Mild (2)				+ (2)				+ (1)							+ (1)	+ (2)
13	F	100.0 (1) 50.0 (2)	+ (1)	+ (2)		Mild (1 & 2)				+ (2)				+ (1)							+ (2)	+ (1)
14	F	75.0		+ (1. 2. 3)		Mod. (1) Mod. (2) Mild (3)				+ (1)				+ (2)	+ (3)				+ (1,2,3)			
15	F	100.0			+	Mild								+								+
16	F	62.5	+			Mild								+								+
17	F	62.5		+ (1)	+ (2)	Mild (1 & 2)									+ (2)		+ (1)		+ (1)	+ (2)		
18	M	75.0	+			Mild												+		+		
19	F	62.5			+ (1 & 2)	Mod. (1) Mild (2)				+ (2)				+ (1)							+ (1)	+ (2)
20	F	62.5		+ (1 & 2)		Mild (1 & 2)									+ (2)	+ (1)				+ (1&2)		
21	F	62.5	+			Mild											+		+			
22	F	62.5		+		Mild											+		+			
23	F	50.0			+	Mild											+		+			
24	M	100.0		+		Mild				+											+	

*In cases in which there was more than one kind of reaction, the numbers in parenthesis designate which kind, as listed in the column headed "Type of Reaction." In Case 3, for example, in following the line across it will be noted that edema, nervousness, thyroid enlargement and skin tags occurred in the first three months. In the last four columns on the same line (under the heading "Fate of Reaction on Continued Treatment") it will be noted that thyroid enlargement and skin tags progressed, that nervousness improved, and that edema disappeared.

normal.[13] No studies relating to the recovery of adrenocortical function after long-term administration have been reported.

Fear has been expressed that the long-continued uninterrupted use of cortisone might produce irreversible atrophy and permanent functional insufficiency of the adrenal cortices. It has been repeatedly observed that regressive morphologic changes may occur in certain ductless glands following the administration of large amounts of the hormone secreted by the gland. In 1938 Ingle, Higgins and Kendall[10] found that atrophy of the adrenal cortex developed in rats which had been given large amounts of cortisone; cytoplasmic bodies were reduced in size and the cells were depleted of lipoid material; the extent of the atrophy resembled those changes which result from anterior pituitary insufficiency in hypophysectomized animals. More recently Sprague and co-workers[13] demonstrated regressive changes in the adrenal cortices, at necropsy, of patients treated with cortisone for a variety of conditions. In some cases the glands weighed considerably less than normal and histologically the cortices, especially the zonae fasciculatae, were narrowed and the cells were devoid of lipoid material. From these pathologic studies there were, of course, no indications that the atrophy produced by cortisone was permanent, but other observations suggest that the anatomic and functional changes are probably reversible. In cases of Cushing's disease which result from a unilateral tumor of the adrenal cortex, the contralateral cortex undergoes distinct atrophy. Following surgical extirpation of the hyperfunctioning tumor, signs of adrenocortical insufficiency may develop immediately unless appropriate postoperative therapy is instituted, but eventually the contralateral cortex recovers and signs of adrenocortical insufficiency disappear.

To determine the recovery rate of adrenocortical function following prolonged uninterrupted cortisone therapy, the drug was withdrawn from 11 patients in the present series who were treated continuously for periods ranging from eight to 14 months. With the hope of minimizing post-cortisone asthenia and the development of acute articular flare-ups, withdrawal was accomplished slowly; the daily dose was gradually reduced over periods of 10 to 16 days. Maintenance doses for these patients had ranged from 37.5 to 100 mg. per day. The following tests of adrenocortical function were made: (1) response of circulating eosinophils to a single 25 mg. dose of pituitary adrenocorticotropic hormone (ACTH) (test of Thorn, Forsham, Pruntz and Hills[15]); (2) urinary excretion of 17-ketosteroids; (3) urinary excretion of corticosteroids (11-oxysteroids). The tests were performed while usual maintenance doses were being continued, 48 hours following complete cessation of the hormone, and every two to three weeks thereafter until the determinations returned to accepted normal values.

Details of this study will be reported separately.[5] As gauged by the response of circulating eosinophils to adrenocorticotropic hormone (ACTH), adrenocortical function was depressed in each case during the administration of cortisone—a decrease in eosinophils, four hours after a 25 mg. injection of ACTH, either did not occur or was definitely less than the accepted normal decrease of 50 per cent. At varying intervals after cessation of treatment, adrenal function, as indicated by this test, recovered. Following withdrawal, the eosinophil response gradually improved, becoming normal within 10 to 80 days in every case. There appeared to be no direct correlation between the degree of initial unresponsiveness or the rate of functional recovery with the length of cortisone administration, the size of the maintenance dose or the completeness of clinical improvement during treatment.

COMMENT

With the uninterrupted administration of cortisone acetate it has been possible to preserve satisfactory improvement for periods of six to 15 months in approximately two-thirds of cases initially started on treatment. Major degrees of suppression could not be supported in the remaining one-third of cases for several reasons. The most common detriment to good antirheumatic effect was the intervention of objectionable hormonal side effects; their appearance often necessitated lowering of the dosage to levels insufficient to uphold adequate clinical improvement. A few patients had gradual deterioration of improvement, and eventual refractoriness to the drug developed in two patients. Despite large suppressive doses of the hormone, effective response could not be established in some cases. However, massive doses (150-200 mg. per day) of cortisone for long periods were not used even in resistant cases, as in the authors' experience such amounts have almost invariably led to the development of troublesome signs of hormonal excess. The authors' attitude in regard to dosage for long-continued treatment with cortisone has been as follows: to employ amounts short of serious hormonal side reactions; to continue therapy if the arthritis can be satisfactorily controlled with safe doses—if not, to stop administration unless the patient is content with a minor degree of improvement.

Unfortunately the poorest results, percentagewise, have been in the more severe cases of rheumatoid arthritis in which relief was most needed. Actually less than one-half of the original group of cases graded as severe have remained well-controlled for long periods. The failures in this group have been due principally to the fact that large doses of the hormone are required for satisfactory control and often it is not possible to give such doses without provoking signs of hypercortisonism; frequently a compromise betwen good antirheumatic effect and safety of administration must be made. It is apparent that for many patients with severe disease other measures designed to alter the activity of the disease will be needed in combination with cortisone if superior results are to be attained. At present the combined use of gold salts and cortisone is being

investigated in the hope that chrysotherapy may subdue part of the disease activity so that smaller, and safer, doses of the hormone will suffice to suppress the rest. Several schemes of administration are being tried by other investigators[9]: (1) repeated short courses of cortisone; (2) short courses of cortisone alternating with short courses of ACTH; (3) continuous combined use of cortisone and ACTH; (4) combined use of cortisone and ACTH in short courses; (5) simultaneous use of cortisone with other steroids. Evaluation of the merits of these various plans cannot be made at this time and must await the conclusion of investigative studies now in progress.

Serious hormonal side reactions have been largely avoided during the prolonged use of smaller maintenance doses of cortisone. Although numerically they have occurred frequently—in 40 per cent of cases—most have been of minor order and many have been transient. Their appearance has been disadvantageous chiefly because they may force reduction in dosage to the sacrifice of clinical response. Certainly a hormone with less tendency to produce adverse reactions, or one with equal liabilities but greater therapeutic effectiveness milligram for milligram, would be an advantage in the practical management of patients.

As other investigators have noted, a definite suppression of adrenocortical function develops during cortisone therapy. If the eosinophil response to ACTH is a valid test of adrenocortical function, it appears that the depressed function is temporary and the adrenal cortices recover even after replacement therapy has been given uninterruptedly for periods up to 14 months. Whether irreversible changes might develop in the adrenal cortex or anterior pituitary gland after continuous administration for longer periods cannot yet be answered. No evidence has evolved from studies by the authors to indicate that irreversible damage has been produced in other organs or tissues.

Never before have such powerful antirheumatic weapons as cortisone and ACTH been available. The ability of the drugs to promote prompt, though transitory, reversal of the activity in rheumatoid arthritis has made them extremely valuable experimental tools, and an unprecedented amount of clinical and laboratory research has already been stimulated. As therapeutic agents, however, various difficulties and dangers attend their use, and as experience widens, their limitations in the treatment of rheumatoid arthritis become more clear. These hormones have not solved the management of this disease—indeed, they have created new problems of their own. In the light of present knowledge, cortisone and ACTH should not be considered as drugs of choice for the treatment of all cases of rheumatoid arthritis. It should not be forgotten that good results may often be obtained from the employment of more conservative measures and from the administration of gold salts. If a fair trial with more usual methods of treatment does not produce improvement, then the use of these newer hormonal substances may be considered. When the physician realizes that neither cortisone nor ACTH will cure rheumatoid arthritis, that their favorable effects consist merely of temporary suppression of the disease, and that in instituting them the patient is committed to prolonged and expensive treatment which is not without hazard, such a conservative attitude will be appreciated. Despite their introduction, rheumatoid arthritis remains a challenge to therapy, and although cortisone and ACTH are powerful adjuvants in the management of some cases, they are not the therapeutic answers for all cases, and apparently are not cures for any case.

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